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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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## Office Action Summary

Application No.

10/581,431

Applicant(s)

BARBAS ET AL.

Examiner

Maher M. Haddad

Art Unit

1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 18 December 2010.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-32 is/are pending in the application.
- 4a) Of the above claim(s) 1-4, 11-14, 17-21, 24, 27 and 30-32 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 5-10, 15, 16, 22, 23, 25, 26, 28 and 29 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)         | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)         | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date. _____  | 6) <input type="checkbox"/> Other: _____                          |

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#### DETAILED ACTION

1. Claims 1-32 are pending.

Upon reconsideration the Examiner has extended the search to cover all the species of Group II.

2. Applicant's election with traverse of Group II, claims 5-10, 15-16, 22-23, 25-26, and 28-29 drawn to an antibody, filed on 12/18/2010, is acknowledged.

Applicant's traversal is on the grounds that the Examiner has not shown that the instant claims must be subjected to restriction and election of species under 37 CFR § 1.475(d) since both the ISR and the IB did not indicate that the application from which the instant US application filed under 35 USC § 371 claims benefit lacked unity of invention. Applicant argues that the ISA/US found that the application complied with the "Unity of Invention" requirements so linked as to form a single general inventive concept under PCT Rule 13.1. Applicants further respectfully submit that since the requirements of PCT Rule 13.1 were met, the claims at issue complied with 37 CFR §§ 1.475 and 1.499. This is not found persuasive because the findings and opinion of the PCT examining authority are not the controlling authority for the USPTO. Further, as stated in the previous Office Action, the different composition of Groups I-III do not have a common core structure or function because there is no 1:1 correlation between DNA, peptide and antibodies. The products are a family of proteins not one particular protein (see PCT Rule 13.2 and example 17 of Annex B) in MPEP. Moreover, a prior art search also requires a literature search. It is an undue burden for the examiner to search more than one invention. Furthermore, Applicant's inventions do not contribute a special technical feature when viewed over the prior art they do not have a single general inventive concept and so lack unity of invention as set forth in the instant Office Action (see the art applied below).

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 1-4, 11-14, 17-21, 24, 27 and 30-32 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions.
4. Claims 5-10, 15-16, 22-23, 25-26, and 28-29 are under examination as they read on an antibody.
5. The specification is objected to under 37 CFR 1.821(d) for failing to provide a sequence identifier for each individual sequence. Figures 4 and 5, on page 7, Table I, page 32 and Table 2, page 33 have described several amino acid sequences that each must have a sequence identifier. Correction is required.
6. The following is a quotation of the second paragraph of 35 U.S.C. 112.

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The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 8, 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- A. Claim 8 is indefinite in the recitation of "RAD3, RAD4, RAD9, RAD11, RAD12, RAD32, RAD34, RAD87, or RAD88" because its characteristics are not known. The use of "RAD3, RAD4, RAD9, RAD11, RAD12, RAD32, RAD34, RAD87, or RAD88" monoclonal antibody as the sole means of identifying the claimed antibody and hybridoma renders the claim indefinite because "RAD3, RAD4, RAD9, RAD11, RAD12, RAD32, RAD34, RAD87, or RAD88" is merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designations to define completely distinct hybridomas or cell lines. It is suggested that an accession number be cited in the claims.
- B. The recitation "having the immunoreactivity of the antibody for claim 8" in claim 10 is indefinite. It is well known in the art that every antiserum has a different specificity because the repertoire of antibodies produced by animal is somewhat different. Thus, it is unclear how one skill in the art would be able to make an antibody with the equivalent immunoreactivity of the RAD3, RAD4, RAD9, RAD11, RAD12, RAD32, RAD34, RAD87, or RAD88 antibody.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claim 8 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that the hybridomas that produce the RAD3, RAD4, RAD9, RAD11, RAD12, RAD32, RAD34, RAD87 and RAD88 antibodies are required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, a deposit of the hybridoma, which produces this antibody, may satisfy first paragraph. See 37 CFR 1.801-1.809.

If the deposits have been made under the terms of the Budapest Treaty, an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating

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that the hybridoma has been deposited under the Budapest Treaty and that the hybridoma will be irrevocably and without restriction or condition released to the public upon the issuance of a patent would satisfy the deposit requirement made herein. See 37 CFR 1.808. Further, the record must be clear that the deposit will be maintained in a public depository for a period of 30 years after the date of deposit or 5 years after the last request for a sample or for the enforceable life of the patent whichever is longer. See 37 CFR 1.806. If the deposit has not been made under the Budapest treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature must be made, stating that the deposit has been made at an acceptable depository and that the criteria set forth in 37 CFR 1.801-1.809, have been met.

If the deposits were made after the effective filing date of the application for a patent in the United States, a verified statement is required from a person in a position to corroborate that the hybridoma described in the specification as filed are the same as that deposited in the depository. Corroboration may take the form of a showing of a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed.

Further, amendment of the specification to disclose the date of deposit and the complete name and address of the depository (ATCC.10801 University Boulevard, Manassas, VA 20110-2209) is required as set forth in 37 C.F.R. 1.809(d).

10. Claims 5-10, 15-16, 22-23, 25-26, and 28-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of an anti- $\alpha$ IIB $\beta$ 3 antibody comprising VH of SEQ ID NOs: 32-38 or RAD3 (VH SEQ ID NO: 36), RAD4, RAD9 (VH SEQ ID NO: 33), RAD11, RAD12 (VH SEQ ID NO: 34), RAD32 (VH SEQ ID NO: 37), RAD34 (VH SEQ ID NO: 35), RAD87 (VH SEQ ID NO: 32) and RAD88 (VH SEQ ID NO: 38) (once the deposit is satisfied), wherein the antibody comprises a heavy chain CDR3 motif Arg-Ala-Asp (RAD).

Applicant is not in possession of the protein claimed in claims 5-10, 15-16, 22-23, 25-26, and 28-29.

The scope of the claim encompasses antibodies comprising SEQ ID NOs: 8, 25-31 within the CDR of the antibody (i.e., Heavy or Light CDR1, CDR2 or CDR3). A subgenus of antibodies that encompass less than the full amino acid sequence of the VH CDR1-3 and VL CDR1-3.

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The specification (§31) discloses the use of phage display to select monoclonal antibodies specific to integrin  $\alpha$ IIB $\beta$ 3 from a synthetic human antibody library based on the randomized HCDR3 sequence VGXXXRADXXXYAMDV (SEQ ID NO:3). The selected antibodies revealed a strong consensus amino acid sequence in HCDR3 (V(V/W)CRAD(K/R)RC) and high specificity toward integrin  $\alpha$ IIB $\beta$ 3 but not to other RGD binding integrins such as integrins  $\alpha$ v $\beta$ 3,  $\alpha$ v $\beta$ 3, and  $\alpha$ 5 $\beta$ 1 (see §31 of the specification). The specification further discloses that ten individual clones that revealed the strongest binding were subsequently analyzed by DNA sequencing. All but one clone contained a disulfide bridge constrained loop in HCDR3 with the consensus sequence V(V/W)CRAD(K/R)RC (SEQ ID NO:4) (Table 2). The exception, clone RAD1, had the corresponding sequence THSRADRRE (SEQ ID NO:19) (Table 2) (see §94 of the specification).

However, the state of the prior art (see e.g. Klimka et al., British Journal of Cancer (2000) 83:252-260, and Beiboer et al., J. Mol., Biol. (2000) 296:833-849) is that methods for screening rely on a two step process where each step results in an antibody. However, each step requires one of the variable domains to be a defined sequence and the defined variable domain provides enough structure to obtain an antibody. The prior art methods do not result in an antibody solely by keeping CDR3 in the VH defined and randomized the rest of the VH and VL domains. The prior art indicated that, in some instances, the CDR3 region is important. However, this region is not solely responsible for binding. The conformation of the other CDRs, as well as framework residues influence binding. The specification discloses that the structural constraints of the selected XXXRADXXX (SEQ ID NO:22) motifs within HCDR3 prompted us to dissect them from the antibody scaffold and evaluate their functional properties (see §103).

However, neither the specification, nor the prior art provides any examples to support the premise that HCDR3 of the VH solely responsible for antigen binding within an antibody. The prior art does not support a definition of an antibody structure solely by defining the HCDR3 sequence of a VH. The specification fails to show that a single HCDR3 specificity of the  $\alpha$ IIB $\beta$ 3 influences the specificity for any antigen binding antibody. The specification fails to establish that by replacing HCDR3 of any antibody (e.g.,  $\alpha$ v $\beta$ 3,  $\alpha$ v $\beta$ 3,  $\alpha$ 5 $\beta$ 1, CD30 or CD47) with SEQ ID NO: 8, 25-31 comprising RAD motif lead to  $\alpha$ IIB $\beta$ 3 selectivity switch in concert with the HCDR3 replacement. Substituting the RAD containing HCDR3 in an antibody has not been shown to lead to  $\alpha$ IIB $\beta$ 3 selectivity switch in concert with the substituted HCDR3. Such teachings were not made part of the specification at the time the invention was made. Accordingly, the disclosed species would not be deemed by one of skill in the art to be representative of the claim scope. The claims do not meet the requirements of 35 USC 112, first paragraph for written description.

Brown et al (J. Immuno. 1996 May, 3285-91 at 3290 and Tables 1 and 2) describes how a one amino acid change in the VH CDR2 of a particular antibody was tolerated whereas, the antibody lost binding upon introduction of two amino changes in the same region. Applicant starting material in the antibody library comprises HCDR3 sequence that with a specific length and RAD motif. It is the logical outcome of the selective anti- $\alpha$ IIB $\beta$ 3 antibodies to contain the RAD motif.

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It is noted that neither Applicant nor the prior art methods do result in an antibody solely by keeping CDR3 in the VH defined and randomizing the rest of the VH and VL domains. The conformation of other CDRs, as well as framework residues influence binding. See e.g., MacCallum et al., J. Mol. Biol. (1996) 262: 732-745 (of record) and Casset et al., BBRC (2003) 307, 198-205 (of record). It is the Examiner's position that a general method of making and identifying antibodies is not enough to describe the procedure for generating and determining whether a given specific binding member will compete for binding to  $\alpha$ IIB $\beta$ 3 with binding activity of another protein comprising RAD. Prior art establishes an insufficient correlation between VH-CDR3 structure and antigen binding. Vajdos et al. (J Mol Biol. 2002 Jul 5;320(2):415-28 at 416) teach that amino acid sequence and conformation of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. Aside from the CDRs, the Fv also contains more highly conserved framework segments which connect the CDRs and are mainly involved in supporting the CDR loop conformations, although in some cases, framework residues also contact antigen. Further, prior art discloses 6 CDRs as being essential structure of the antibody's binding site, and thus when intact, would provide enough structure to define the antibody's binding site (structure / function correlation). Prior art methods for screening rely on a two step process where each step results in an antibody. However, each step requires one of the variable domains to be a defined sequence and the defined variable domain provides enough structure to obtain an antibody. See e.g. Klimka et al., British Journal of Cancer (2000) 83: 252-260 (of record); and Beiboer et al., J. Mol. Biol. (2000) 296:833-849 (of record). Neither Applicant nor the prior art methods do result in an antibody solely by keeping HCDR3 in the VH defined and randomizing the rest of the VH and VL domains.

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3<sup>rd</sup> column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

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Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant is invited to point to clear support or specific examples of the claimed invention in the specification as-filed.

11. Claims 5-10, 15-16, 22-23, 25-26, and 28-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an anti- $\alpha$ IIB $\beta$ 3 antibody comprising VH of SEQ ID NOs: 32-38 or RAD3 (VH SEQ ID NO: 36), RAD4, RAD9 (VH SEQ ID NO: 33), RAD11, RAD12 (VH SEQ ID NO: 34), RAD32 (VH SEQ ID NO: 37), RAD34 (VH SEQ ID NO: 35), RAD87 (VH SEQ ID NO: 32) and RAD88 (VH SEQ ID NO: 38) (once the deposit is satisfied), wherein the antibody comprises a heavy chain CDR3 motif Arg-Ala-Asp (RAD), does not reasonably provide enablement for the antibodies claimed in claims 5-10, 15-16, 22-23, 25-26, and 28-29. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The knowledge in the art of making the genus of antibody that binds human  $\alpha$ IIB $\beta$ 3 using a particular HCDR3 as the starting point is low.

The scope of the claim encompasses antibodies with HCDR3 in the place of HCDR1 or HCDR2, LCDR1-3 as well as a subgenus of antibodies that encompass only HCDR3.

The specification fails to show that a single HCDR3 specificity of the  $\alpha$ IIB $\beta$ 3 influences the specificity for any antigen binding antibody. The specification fails to establish that by replacing HCDR3 of any antibody (e.g.,  $\alpha$ v $\beta$ 3,  $\alpha$ v $\beta$ 3,  $\alpha$ 5 $\beta$ 1, CD30 or CD47) with SEQ ID NO: 8, 25-31 comprising RAD motif lead to  $\alpha$ IIB $\beta$ 3 selectivity switch in concert with the HCDR3 replacement. Substituting the RAD containing HCDR3 in an antibody has not been shown to lead to  $\alpha$ IIB $\beta$ 3 selectivity switch in concert with the substituted HCDR3. Such teachings were not made part of the specification at the time the invention was made.

However, neither the instant specification nor the prior art provide sufficient guidance or direction for one of ordinary skill in the art to make the antibodies encompassed by the breadth of the instant claims.



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With respect to making the genus of anti-human  $\alpha$ IIB $\beta$ 3 antibodies using a particular VH CDR3 as the starting point, e.g., SEQ ID NOs: 8 or 25-31, it is known in the art that antibody-antigen affinity and specificity is a function of not only direct CDR to antigen interactions, but also the interactions of the CDRs with framework residues in the same chain, e.g., VH CDR binding to VH framework residues, and in the opposing chain, e.g., VH CDR binding to VL framework residues. In addition, the CDR residues of each chain can interact with the CDRs of the opposite chain. It is for this reason that antibody humanization protocols, e.g., humanization of a murine antibody, provide extensive guidelines as to the retention of certain murine residues in the context of the human framework so as to preserve this web of interactions, the loss of any one of these interactions having the potential to ablate antibody-antigen binding (see, e.g., Eduardo Padlan, *Mol Immunol.* 1994 Feb;31(3):169-217, in particular column bridging paragraph on page 177; page bridging paragraph pages 178-179 through page 180; pages 201, 204 and Tables 8, 22 and 23 and Adair et al., United States Patent No. 5,859,205, in particular columns 1-6, 9-11 and 27-28).

In the instant case, the claims recite of VH CDR3 of a variable domain, not all the 6 CDRs or the variable domain itself. While CDRs are important for binding and contribute the majority of contact residues with the target antigen, the framework residues are also essential for maintaining the proper antigen-binding conformation of the CDRs and for proper association of the heavy and light chain variable regions.

As such, it appears that making the claimed genus of antibodies would be an unpredictable endeavor requiring far more than routine experimentation because a single HCDR3 comprises less than a majority of the residues important for antigen recognition. Moreover, art techniques for identifying other variable domains by screening require an intact variable domain comprising CDRs interspersed between frameworks as the starting structure to be taken through the screening assay. The instant claims recite less than this minimum structure that is required for screening, and the instant specification fails to provide sufficient direction or guidance as to the breadth of the frameworks that can accommodate the claimed CDRs while simultaneously providing appropriate structure to pair with a light chain variable domain capable of acting with heavy chain variable domain to create a  $\alpha$ IIB $\beta$ 3 binding site.

The state of the prior art is such that it is well established in the art that the formation of an intact antigen-binding site of antibodies routinely requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding of the antibody to its target epitope (Paul, *Fundamental Immunology*, 3<sup>rd</sup> Edition, 1993, pp. 292-295, under the heading "Fv Structure and Diversity in Three Dimensions"). The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce an antibody having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional

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antigen binding sites (Paul, page 293, first column, lines 3-8 and line 31 to column 2, line 9 and lines 27-30, IDS-C18). Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc. Natl. Acad. Sci. USA, 79(6):1979-1983, March 1982 (IDS-C37)). Rudikoff et al teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function.

While there are some publications, which acknowledge that CDR3 is important, the conformations of other CDRs as well as framework residues influence binding. MacCallum et al (J. Mol. Biol., 262, 732-745, 1996, IDS-C14) analyzed many different antibodies for interactions with antigen and state that although CDR3 of the heavy and light chain dominate, a number of residues outside the standard CDR definitions make antigen contacts (see page 733, right col.) and non-contacting residues within the CDRs coincide with residues as important in defining canonical backbone conformations (see page 735, left col.). The fact that not just one CDR is essential for antigen binding or maintaining the conformation of the antigen binding site, is underscored by Casset et al (Biochemical and Biophysical Research Communications, 307:198-205, 2003, IDS-C6), which constructed a peptide mimetic of an anti-CD4 monoclonal antibody binding site by rational design and the peptide was designed with 27 residues formed by residues from 5 CDRs (see entire document). Casset et al also states that although CDR H3 is at the center of most if not all antigen interactions, clearly other CDRs play an important role in the recognition process (page 199, left col.) and this is demonstrated in this work by using all CDRs except L2 and additionally using a framework residue located just before the H3 (see page 202, left col.). Thus, the state of the art recognized that it would be highly unpredictable that an antibody comprising less than all six CDRs of a parental antibody. Thus, the minimal structure which the skilled artisan would consider predictive of the function of binding the  $\alpha$ IIB $\beta$ 3 includes six CDRs (three from the heavy chain variable region and three from the light chain variable region) from parental antibody RAD3, RAD4, RAD9, RAD11, RAD12, RAD32, RAD34, RAD87, or RAD88 in the context of framework sequences which maintain their correct spatial orientation have the requisite  $\alpha$ IIB $\beta$ 3 binding function. One of ordinary skill in the art could not predictably extrapolate the teachings in the specification, limited to antibodies that comprise both the heavy chain variable region and the light chain variable region or all six CDRs of RAD3, RAD4, RAD9, RAD11, RAD12, RAD32, RAD34, RAD87, or RAD88 that binds the  $\alpha$ IIB $\beta$ 3 to make and use antibodies that comprise fewer than all six CDRs from parental antibody RAD3, RAD4, RAD9, RAD11, RAD12, RAD32, RAD34, RAD87, or RAD88 i.e., antibodies comprising a CDR of SEQ ID NOs: 8 or 25-31 each having less than the required three CDRs as broadly as claimed. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one particular species, what other species will work. See MPEP 2164.03. One of skill in the art would neither expect nor predict the appropriate functioning of the anti- $\alpha$ IIB $\beta$ 3 antibodies as broadly as is claimed.

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It is also known that given one specified variable domain, either heavy or light, the skilled artisans can screen libraries to identify other variable domains that will pair with the starting variable domain and maintain antigen specificity (Portolano et al., J Immunol. 1993 Feb 1;150(3):880-7, see entire document, particularly figure 1). Thus, it is known in the art that artisans can screen for other variable domains that will ensure a functional antibody of defined antigen specificity if a full variable domain is used in the screening assay. Accordingly, the specification is enabled for the anti- $\alpha$ IIB $\beta$ 3 antibodies comprising VH comprising SEQ ID NOS:32-38.

Furthermore, regarding in vivo methods which rely on generally unpredictable mechanisms, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling (MPEP 2164.03)." The MPEP also states that physiological activity can be considered inherently unpredictable.

Also, at issue is whether or not the claimed composition claimed in claims 22-23 would function as pharmaceutical composition. In view of the absence of a specific and detailed description in Applicant's specification of how to effectively use the pharmaceutical composition as claimed, and absence of working examples providing evidence which is reasonably predictive that the claimed pharmaceutical composition are effective for in vivo use, and the lack of predictability in the art at the time the invention was made, an undue amount of experimentation would be required to practice the claimed pharmaceutical composition with a reasonable expectation of success.

At issue is whether the claimed anti- $\alpha$ IIB $\beta$ 3 antibodies would function to treat/prevent thrombosis in pulmonary embolism, transient ischemic attacks (TIAs), deep vein thrombosis, coronary bypass surgery, and surgery to insert a prosthetic valve or vessel in autologous, non-autologous or synthetic vessel graft in claims 25-25 and 28-29. The exemplification is drawn to the use of the anti- $\alpha$ IIB $\beta$ 3 integrin antibody to inhibit the interaction between integrin  $\alpha$ IIB $\beta$ 3 and fibrinogen and platelete aggregation (See ¶97, Fig. 4 and table 3). "First, although appellants' specification describes certain in vitro experiments, there is no correlation on this record between in vitro experiments and a practical utility in currently available form for humans or animals. It is not enough to rely on in vitro studies where, as here, a person having ordinary skill in the art has no basis for perceiving those studies as constituting recognized screening procedures with clear relevance to utility in humans or animals" (emphasis added). Ex parte Maas, 9 USPQ2d 1746.

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In Rasmusson v. SmithKline Beecham Corp., 75 USPQ2d 1297-1303 (CAFC 2005), the court states “If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to “inventions” consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the 'inventor' would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis.”

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

13. Claims 10, 15-16, 23, 26 and 29 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent 7,812,136 B2.

The `136 patent teaches and claims an Antibody of human origin, wherein said antibody inhibits platelet aggregation and has a greater binding affinity to the activated state of platelet integrin receptor GPIIb/IIIa than to the inactive conformation of the platelet integrin receptor GPIIb/IIIa, wherein the antibody comprises the heavy and light chain variable domains of the amino acid sequence of SEQ ID NO: 159 (see patented claims 1-7). The `136 patent teaches a pharmaceutical composition containing the antibody. The administration of the pharmaceutical composition may be orally or parenterally (e.g. topically, intra-arterially, intramuscularly, subcutaneously, intramedullary, intrathecally, intraventricularly, intravenously, intraperitoneally or intranasally). The suitable dosage will be determined by the medical doctor and is dependent on various conditions (see II 7, lines 25-50).

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Claim 26 is included because when a claim recites using an old composition or structure (e.g.  $\alpha$ IIB $\beta$ 3-specific antibodies) and the use is directed to a result or property of that composition or structure (treatment of thrombosis), then the claim is anticipated. See MPEP 2112.02. Also, see Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc. 58 USPQ2d 1508 (CA FC 2001); Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

Since the office does not have a laboratory to test the reference antibodies, it is applicant's burden to show that the reference antibody does not compete/immunoreact with binding activity of another protein comprising RAD motif recited in the claims 10 and 15-16. See *In re Best*, 195 USPQ 430, 433 (CCPA 1977); *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and *In re Fitzgerald et al.*, 205 USPQ 594 (CCPA 1980).

The reference teachings anticipate the claimed invention

14. Claims 10, 15-16, 23, 26 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Quinn et al (Circulation. 1999;99:2231-2238.).

Quinn et al teaches in vitro binding of monoclonal antibodies, LYP18 (Mab1) and 4F8 (Mab2), to the GPIIb/IIIa ( $\alpha$ IIB $\beta$ 3) complex, was characterized using purified receptor and to platelets by flow cytometry. Patients undergoing coronary angioplasty received a single 20 mg dose of the oral GPIIb/IIIa antagonist, xemilofiban, or matching placebo, and antibody binding was compared with inhibition of platelet aggregation. Mab1 and Mab2 were bound to purified GPIIb/IIIa and to unoccupied, inactivated receptor on platelets. Mab2 identified the  $\beta$ 3 subunit, whereas Mab1 was complex-specific. Neither antibody interfered with the other's binding, suggesting that they identified distinct sites. Mab1 binding was inhibited by abciximab (anti- $\alpha$ IIB $\beta$ 3 antibody) in a dose dependent manner ( $IC_{50}$ ,  $0.85 \pm 0.1 \mu\text{g/mL}$ ), whereas Mab2 binding was unaffected. Platelet aggregation to adenosine diphosphate ( $20 \mu\text{mol/L}$ ) fell to  $3 \pm 3\%$  of baseline in line with the inhibition of Mab2 binding (correlation coefficient 0.8,  $P < 0.0001$ ). The references antibodies would have the immunoreactivity/compete with the antibodies recited in claims 10/16 in the absence of evidence to the contrary.

Claim 26 is included because when a claim recites using an old composition or structure (e.g.  $\alpha$ IIB $\beta$ 3-specific antibodies) and the use is directed to a result or property of that composition or structure (treatment of thrombosis), then the claim is anticipated. See MPEP 2112.02. Also, see Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc. 58 USPQ2d 1508 (CA FC 2001); Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

Since the office does not have a laboratory to test the reference antibodies, it is applicant's burden to show that the reference antibody does not compete/immunoreact with binding activity

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of another protein comprising RAD motif recited in the claims 10 and 15-16. See *In re Best*, 195 USPQ 430, 433 (CCPA 1977); *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and *In re Fitzgerald et al.*, 205 USPQ 594 (CCPA 1980).

The reference teachings anticipate the claimed invention.

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

January 5, 2011

/Maher M. Haddad/  
Primary Examiner,  
Art Unit 1644